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Revision of the General Pharmaceutical Legislation: Impact Assessment of Key Orphan Proposals on Member States

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Executive Summary

While the revision of the General Pharmaceutical Legislation (GPL) targets EU-level frameworks and processes, proposed changes are sure to have immediate as well as downstream consequences at the country level. This paper explores these potential consequences, focusing on a selection of proposals by the European Commission aimed at improving access and affordability of orphan medicinal products (OMPs).

Key findings highlight:

- Risks to future OMP development and availability in Europe via proposed reductions in key incentives (although these may help bring down prices in the short term),
- Challenges with the calibration and predictability of conditional supplementary incentives aimed at encouraging OMP development in areas of high unmet need and faster launch of medicines across Europe,
- Potential impact on national pricing and reimbursement (P&R) processes due to changes impacting evidence availability, and risk that this fails to align with country needs and priorities.

The revised GPL that is ultimately adopted will set the stage for the European pharmaceutical market for decades to come, particularly for OMPs which are more reliant on incentives to be viable for development and launch in the region. It is therefore critical that revisions are calibrated to meet Member States' needs and assure future availability of these products in Europe.

Glossary of abbreviations

EU	European Union
GPL	General Pharmaceutical Legislation
HTA	Health technology assessment
HUMN	High unmet medical need
IP	Intellectual property
NIH	National Institute for Health
OME	Orphan market exclusivity
OMP	Orphan medicinal products
P&R	Pricing and reimbursement
R&D	Research and development
ROI	Return on investment
SME	Small and medium enterprises
UMN	Unmet medical need

Introduction

Rare diseases affect millions of people across Europe[1] and are seen as a political priority at both EU and national levels.[2,3] Despite the tremendous progress in therapeutics and quality of life achieved since the introduction of the Orphan Regulation 24 years ago, unmet need in rare diseases continues to be high and access remains a challenge across Europe.[4]

The General Pharmaceutical Legislation (GPL) is critical in shaping the pharmaceutical environment in Europe as it governs the granting of marketing authorisations and intellectual property (IP) incentives for medicines, including those for rare diseases. A revision of the GPL was triggered in March 2021 to address various shortcomings identified with the current legislation, including those related to access and affordability of orphan medicinal products (OMPs) for rare diseases.[5] The revised GPL that will ultimately be adopted will set the stage for the European pharmaceutical market for decades to come.

The purpose of this assessment is to explore both immediate and future possible consequences of the revision from the perspective of Member States with a particular focus on OMP access and affordability. Given that OMPs generally rely on incentives within the GPL to be viable for development and launch in Europe, any negative or unintended consequence of proposals risks hampering innovation and availability of new products to address the significant unmet need which remains.

The scope of this assessment focuses on three key proposals by the European Commission aimed at improving OMP access and affordability:

- Changes to the OMP incentive framework to balance innovation with affordability and encourage development in areas of high unmet need,
- Introduction of launch conditionality provisions to encourage timely, equitable access,
- Introduction of reporting requirements to achieve transparency of public contributions to research and development (R&D) financing to promote affordability.

Policy context

The GPL was first established in 1965 with the dual objective of preserving public health and harmonising the European market for medicines. It has since been complemented by dedicated regulations to address the specific characteristics of certain medicines, such as for advanced therapies or those targeting rare diseases or children. Among these, the Orphan Regulation sets out the legal framework governing OMPs authorised for the treatment of rare diseases in Europe.[6]

First adopted in 1999, the Orphan Regulation was established to encourage the development and launch of medicines to treat small populations, based on the recognition that the commercial challenges to develop these medicines are greater than for common conditions. Inspired by the success of similar legislations in

[1] Pakter, P. (2024). Rare disease care in Europe – Gaping unmet needs. Available here.
[2] European Commission (2014). Implementation report on the Commission Communication on Rare Diseases: Europe's Challenges. Available here.
[3] Rare2030 (2021). Recommendations from the Rare 2030 Foresight Study: The Future of Rare Diseases Starts Today. Available here.
[4] EURORDIS (2023). Revisions for the better: How Europe should boost the development of rare disease medicines. Accessed 17 April from here.
[5] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 1/2). Available here.
[6] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 1/2). Available here.

the US and Japan, the Orphan Regulation laid out the procedure and criteria for designating an OMP as well as the incentives to encourage their development and authorisation in Europe.[7]

The GPL, including the Orphan Regulation, was opened for revision in March 2021 with the aim of addressing identified challenges within the current legislation and to ensure alignment with the new Pharmaceutical Strategy for Europe that was adopted in November 2021 partly in response to the COVID-19 pandemic.[8] In their Impact Assessment of the existing Orphan Regulation, the Commission deemed it successful in fostering the R&D towards, and availability of, rare disease medicines, but falling short in terms of incentivising development in areas of greatest unmet medical need (UMN), safeguarding affordability for healthcare systems, and supporting broad and equitable patient access across all Member States.[9] The revision seeks to address these points and enhance European's global competitiveness.

This paper dates to March 2024, and focuses on key proposals adopted by the Commission for a revised GPL. It also considers as secondary context the draft proposed amendments by the European Parliament to the Commission's proposal.[10,11]

Assessment methodology

The goal of this assessment is to highlight immediate and future possible consequences of proposals from the view of Member States. A two-step approach was taken:

Step 1: Key Commission documents (impact assessments, proposals) were reviewed to understand the Commission's depiction of the specific 'problem' prompting the revision, objectives of the intervention, nature of their proposals, and intervention logic underpinning these.

Step 2: A qualitative assessment was conducted to examine the potential impact of proposals on Member States according to the following three areas:

- **Area 1. Capacity to improve OMP access and affordability in the short term**. Improving access and affordability of OMPs is generally viewed a priority among Member States and a goal of the Commission's Pharmaceutical Strategy. Proposals were assessed in terms of their capacity to achieve this objective in relation to products which are already or will shortly be launched in Europe. This was determined via qualitative examination of the strength of the underlying logic connecting proposals to their intended outcomes.
- **Area 2. Impact on future availability of innovative OMPs in Europe**. It is understood that there are a multitude of complex factors which impact timely access to innovative therapies.[12] Yet, a necessary precondition to access in Europe is that the industry drug sponsor elects to develop and launch a product in the region and seek reimbursement from national authorities. The GPL plays a crucial role in shaping the environment for innovation in Europe. Hence, proposals were qualitatively assessed in terms of their potential to impact incentives for industry to invest in the development and launch of OMPs in Europe in a timely manner relative to other regions (e.g. the US).
- **Area 3. Implementation considerations for Member States.** Though proposals sit at the EU

[7] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available here.
[8] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 1/2). Available here.
[9] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 2/2). Available here.
[10] European Parliament (2023). Draft Report (2023/0131(COD)). Available here.
[11] Note: As a next step, the final proposals adopted by the Commission and Parliament will undergo review by the European Council, followed by a tripartite dialogue to reconcile divergences in proposals and adopt a final version for implementation.
[12] EFPIA (2022). The root cause of unavailability and delay to innovative medicines. Available here.

regulatory level, they may still have practical consequences for some Member States. Key areas considered in this assessment include changes in Member State responsibilities (e.g., reporting requirements), potential to impact pricing and reimbursement (P&R) processes and frameworks or evidence availability, and possible misalignment with Member State priorities.

Proposed revisions to the OMP incentive framework

(i) Context and problem

Within the current Orphan Regulation, products qualify for orphan status if they fulfil the following criteria:

- The disease affects no more than five in 10,000 persons,
- The condition is life-threatening or chronically debilitating and lacking satisfactory treatment or the product is of significant benefit (defined as a clinically relevant advantage or a major contribution to patient care) versus existing treatments.[13]

Qualifying products can benefit from several incentives, including ten years of orphan market exclusivity (OME), which grants protection from market competition by similar medicines with the same indications. This is applied at indication level, so each approved therapeutic indication benefits from its own separate OME period.[14]

In the nearly 25 years the Orphan Regulation has been in place, there has been a significant increase in the availability of orphan medicines in Europe. Indeed, only eight 'orphan-like' medicines were authorised prior to the year 2000[15] versus more than 200 orphan medicines as of 2023.[16] In their evaluation of the Orphan Regulation, the Commission acknowledged its contribution to fostering the development of new treatments for rare diseases, but also raised several issues, including two related to access and affordability:[17]

- First is that the affordability of OMPs is a challenge for healthcare systems. This is seen to be driven by the price of innovative medicines combined with limited entry of generic and biosimilar products in rare diseases, which is in part attributed to sequential OME durations for new indications.
- Second is persistent innovation gaps in high unmet medical needs (HUMN) in rare diseases, which is seen to be a result of the high commercial risk in areas of HUMN, and thus industry prioritising R&D in more lucrative and less risky areas.

The specific objectives outlined by the Commission for the revision to address these challenges are:[18]

- To create a balance where OMP innovation is rewarded, and faster market entry of generic and biosimilar medicines is facilitated,
- To direct development of new OMPs towards areas of HUMN.

[13] European Medicines Agency (n.d.). Legal framework: orphan designation. Accessed 10 April 2024 from here.
[14] European Medicines Agency (n.d.). Orphan incentives. Accessed 10 April 2024 from here.
[15] EFPIA (2024). Imagining a future where rare diseases patients have a better chance at a healthy life. Accessed 10 April 2024 from here.
[16] European Commission (n.d.). Orphan medicinal products. Accessed 10 April 2024 from here.
[17] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 2/2). Available here.
[18] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 2/2). Available here.

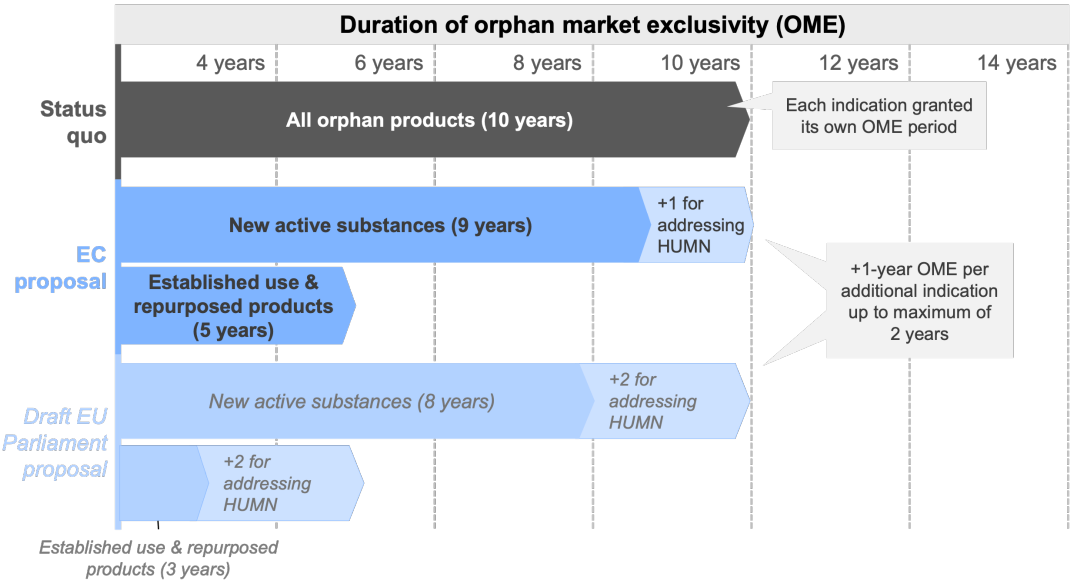
(ii) Commission proposals

Towards achieving these objectives, the Commission proposes several revisions to the existing legal framework governing OMPs:[19]

- Orphan designation:
  - Apply a seven-year temporal validity to orphan designation (presently unlimited).
  - Maintain the current prevalence criteria but give the Commission discretion to amend on a case-by-case basis for scientific reasons (e.g., for conditions with short duration and high mortality, where incidence may be more appropriate).
  - Redefine 'significant benefit' so it must relate to a substantial part of the target population (presently it can apply to any proportion).

- Orphan incentives:
  - Offer a single marketing authorisation and associated OME period for each active substance (presently each indication qualifies for its own period of OME).
  - Introduce a modulated system of OME where novel products addressing a HUMN[20] receive the same OME duration as today and other products receive less (echoed in draft Parliament proposals, see Figure 1). Note that Qualifying for HUMN would require evidence of 'exceptional therapeutic advancement' versus existing treatment options that results in 'meaningful reduction' in morbidity or mortality for the relevant patient population.

Figure 1. Comparison of current OME period versus those proposed by the Commission and draft proposal by the Parliament



Note: Extensions for Paediatric investigation plan not shown.
Abbreviations: EC: European Commission; EU: European Union; HUMN: High unmet need; MA: Marketing authorisation; OME: Orphan market exclusivity.

Alongside, the Commission proposes a few changes to existing regulatory frameworks for generic and biosimilar products:[21]

[19] European Commission (2023). Proposal for the Pharmaceutical Regulation. Available here.
[20] Note that under the Commission's proposal all OMPs would qualify as addressing an UMN as default, since fulfilling criteria for the designation automatically implies that proposed criteria for UMN are fulfilled as well.
[21] European Commission (2023). Proposal for the Pharmaceutical Directive. Available here.

- Enhance those regulatory benefits which already exist to support generic and biosimilar competition by facilitating the development and launch of these products i.e.:
  - Simplifying the system of authorisation of these products (namely, removal of the requirement for risk management plans and better recognition of interchangeability of biosimilars).
  - Broadening and clarifying the scope of the Bolar exemption (which permits necessary studies for obtaining regulatory approval during IP protection period of reference medicines[22]) to encourage harmonised application by Member States (namely, specifying that trials for P&R are included in the exemption, even when performed by third-party suppliers or service providers).[23]

(iii) Impact assessment and discussion

Impact area 1: Capacity to improve OMP access and affordability in the short term:

The Commission's objective with these proposals is to balance OMP innovation with affordability, while also driving innovation in areas of HUMN. A key assumption underpinning their proposal is that affordability will be improved by achieving lower prices via increased generic and biosimilar competition. Indeed, encouraging use of generic drugs and biosimilars are effective tools to manage health care budgets and affordability, as it generates cost savings to health systems.[24] However, in rare diseases, biosimilar competition has shown to be limited. The Commission attributes this in part to the OME 'blocking' their entry. While this is partly true, it is also a result of the clinical and commercial challenges in developing and launching biologics in rare conditions.[25] These include challenges in the development of biosimilars arising from the scarcity and high cost of comparator drug supplies and from small patient populations, as well as the commercial attractivity of such niche markets. Current proposals may be insufficient to address such barriers in certain circumstances (e.g. ultra-rare conditions with high-cost treatments).

Another key assumption underpinning the Commission's proposal around modulated OME is that it will preserve innovation in areas of HUMN and accelerate generic / biosimilar entry in remaining areas. In practice, results are likely to be mixed. Reducing OME may indeed result in price reductions sooner with earlier biosimilar / generic entry, resulting in cost savings and better affordability for Member States. For manufacturers, however, the last years of protection are the most profitable ones as that is when the peak uptake has been reached. As a result, removing the last years of OME would have a disproportionate negative impact on overall revenues. Over the coming years, this may disincentivise manufacturers from launching their products in Europe (or specific markets within) if the potential return on investment (ROI) is not sufficient to warrant the cost, time, and risk of doing so. For products which have already been approved in Europe, it may drive manufacturers to increase their prices at launch to account for the lost revenues owing to the shorter OME period, making them less affordable and hence available to patients.

A third assumption underpinning their proposal is that an OME in line with the status quo would be sufficient to drive development in areas which have historically been underserved. However, surely these areas would require a higher level of incentives, given many are ultra-rare and/or paediatric, and therefore face additional hurdles in their development and commercialisation.[26] The Commission might anticipate that reducing OME in non-HUMN areas will drive investment to those remaining, though this is unlikely owing to the generally higher

[22] European Commission (2020). Commission Staff Working Document – Evaluation of the Regulation No 469/2009. Available here.
[23] Blaney and Dirkzwager (2023). EU Pharma Legislation Review Series: Bolar Exemption under Patent Rights. Accessed 10 April 2024 from here.
[24] Wouters et al. (2017). Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. Available here.
[25] Dowlat (2016). The opportunities and challenges of biosimilar orphans. Available here.
[26] Neez et al. (2021). Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions. Available here.

risk and challenge in these areas and the fact that the proposed extension is only sufficient to recover the reduced OME from baseline.

Impact area 2. Impact on future availability of innovative OMPs in Europe:

A related challenge with the Commission's proposal is the subjectivity of HUMN criteria. It is yet unclear, for instance, what qualifies as 'significant benefit / therapeutic advancement' or 'substantial reduction' in morbidity or mortality. This hampers the predictability of its application, introducing risk for industry that the OME extension may not ultimately be granted. Industry not being confident that the extension will be granted is, in terms of driving investment decisions, the same as the extension not existing.

Recall the existing orphan incentive framework was established for the purpose of encouraging the development and launch of products for rare diseases, and per the Commission's impact assessment, has been proven effective at doing this.[27] The fact that the Commission has proposed to retain certain key elements within the current Orphan Regulation is promising for future OMP availability in Europe. A pivotal example of this is the maintenance of the existing prevalence threshold to qualify for orphan designation, which is a key factor in keeping European regulation in step with other regions as well as ensuring predictability and continuity for industry.

However, there are several areas within the Commission's proposal which risk eroding the environment for OMP development and launch in Europe:

- Incentives are reduced: The baseline duration of OME would be lower for most products, meaning it will be harder for market authorisation holders to achieve sufficient ROI to warrant the time, cost, and risk of developing OMPs for and launching them in Europe. This is especially true for follow-on indications, which would no longer qualify for their own OME period, even though they still require their own development programme and commercial launch (with associated time, cost, and risk). Under the Commission's proposal, expansion into new indications beyond the first three would no longer be encouraged.
- Incentives are less certain: Eligibility for OME extension for addressing a HUMN is very uncertain owing to the lack of clarity around the criteria. Further, the proposal for seven-year temporal validity of orphan designation introduces the risk that sponsors lose the designation and associated benefits when seeking marketing authorisation if the product is not developed or launched within this timeframe. This is frequently the case for rare diseases, where development programmes may be complicated and delayed owing to the scarcity of patients.[28]

A recent analysis estimated that the Commission's proposals would hamper the development of 45 products in Europe between 2020 and 2035, equating to a decrease in innovation of 12%.[29] Industry stakeholders have cited these concerns and predicted their implications: EUCOPE foresee that proposals will disproportionately impact small and medium enterprises (SMEs) as well as undermine innovation for rare diseases in Europe and EFPIA warns that proposals will weaken Europe's position as a driver of innovation relative to other regions.[30,31] Reduced industry investment in Europe may result in a reduction in critical knowledge, capability, and infrastructure underpinning the development and delivery of these treatments, which would further hamper future availability of new innovations in rare diseases for Member States and patients.

[27] European Commission (2020). Commission Staff Working Document – Joint evaluation of Regulations No 1901/2006 and 141/2000. Available here.
[28] The Lancet (2019). Spotlight on rare diseases. Available here.
[29] Neez and Hutchings (2023). Revision of the Orphan Regulation: Estimated impact on incentives for innovation of changes proposed by the European Commission. Available here.
[30] EUCOPE (2022). EUCOPE letter on the revision of the general pharmaceutical and OMP legislation. Available here..
[31] Dolon (2023). Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available here..

At the Member State level there are two key implications to be aware of:

- First, the anticipated reduction in the availability of new OMPs will result in fewer options and worse outcomes for patients versus other regions where those products are available, to the detriment of Member State health systems and society.
- Second, projected reductions in Europe's competitiveness is likely to be associated with a decline in R&D activity, translating to reductions in the broader economy and employment. Presently, Europe's pharmaceutical sector employs ~840,000 people (125,000 of whom work in R&D) and generates an estimated €175 billion trade surplus, significantly impacting the EU's overall trade balance. [32]

Impact area 3. Implementation considerations for Member States:

The proposed introduction of regulatory definitions of UMN and HUMN presents the potential for misalignment with Member States and practical challenges resulting from this. Variations in UMN definition risk increasing the gap between expectations and decisions made at regulatory versus national level. In a joint response to the Commission's proposal, national health technology assessment (HTA) bodies stressed the importance of their being consulted in the development of regulatory definitions of UMN and shared concerns over increased uncertainty in the assessment of medicines owing to the large number of alternative and accelerated regulatory pathways proposed.[33]

Proposal on launch conditionality

(i) Context and problem

In their impact assessment of the Orphan Regulation, the Commission identified unequal access to medicines in the EU as a key challenge to address with the revision. The Commission cite considerable variation in market uptake of OMPs across Member States and an estimate that in a majority of Member States only about half of authorised OMPs are presently accessible to patients that could benefit from these medicines.[34]

This problem of unequal access to OMPs across Member States is seen to be primarily driven by the fact that medicines are not launched in all Member States. Indeed, neither the Orphan Regulation nor the GPL impose any obligation or incentives for marketing authorisation holders to launch their products in all Member States, nor are there any specific requirements when withdrawing those products for commercial reasons. The Commission cite the tendency of pharmaceutical companies to favour launching in Member States with higher willingness to pay as a key element in this equation of unequal access, with another being variation and delays in Member States' individual HTA and P&R processes.[35]

In view of this challenge, a specific objective of the Commission's proposal is to ensure all patients across the EU have timely and equitable access to safe, effective and affordable medicines.[36]

[32] EFPIA (n.d.). Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available here..
[33] Heads of HTA Agencies Group (2024). Joint position statement on the Commission's proposal. Available here.
[34] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 2/2). Available here.
[35] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 2/2). Available here.
[36] European Commission (2023). Proposal for the Pharmaceutical Directive. Available here.

(ii) Commission proposals

To address the challenge of unequal and delayed access to medicines in Europe, the Commission propose to offer two IP incentives for OMPs, conditional on the OMP being launched and supplied in all 27 Member States within two years (three years for SMEs) of receiving market authorisation:[37]

- Additional two years of regulatory data protection (applicable to all medicines).
- Additional 12 months of OME (applicable only to OMPs, and in effect the stronger and more important form of IP protection from the perspective of the market authorisation holder).

Member States would have the option to waive the condition of launching within two years in their territory, for example if meeting the condition is considered materially impossible.

Note that the European Parliament propose quite a different approach in the current draft amendments to the Commission's proposal. In their view, marketing authorisation holders should be required to submit a 'good faith application' for P&R within two years of authorisation in all Member States that have requested the product (extended to four years for SMEs, non-profits, and companies with fewer than seven market authorisations in the EU).[38] This removes the conditional data protection benefit proposed by the Commission and requires that Member States take an active role in requesting the submission of the product on that timeframe. No detail is provided on what constitutes a 'good faith' application, nor what would happen if the marketing authorisation holder failed to submit a dossier in all Member States that have requested it within the designated timeframe.

(iii) Impact assessment and discussion

Impact area 1. Capacity to improve OMP access and affordability in the short term:

The Commission's specific objective for this proposal is to promote timely and equitable access to centrally approved medicines for all patients across the EU.

There are two general assumptions underpinning the Commission's proposal:

- The first is that market launch within two years in all 27 Member States is feasible, though experience would suggest that this is largely unattainable in the current system. Average reimbursement timelines for innovative treatments vary dramatically across the EU, with estimates ranging from a few months in some countries to well over two years in others.[39]
- The second is that obtaining reimbursement within two years can be determined by industry, though this too is not the case. An analysis by EFPIA examining root causes of delayed access identified numerous potential factors which are not under developers' control, including time to initiating HTA and P&R processes, length and contingencies within these processes, and resource constraints to implement decisions.[40] Although the introduction of Joint Clinical Assessment per the new Regulation on HTA seeks to remedy discrepancies and accelerate country P&R timelines, a certain degree of variation and delays are very likely to persist across Member States given that recommendations are not binding.[41]

[37] European Commission (2023). Proposal for the Pharmaceutical Directive. Available here.
[38] European Parliament (2023). Draft Report (2023/0131(COD)). Available here.
[39] EFPIA (2022). The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines. Available here.
[41] EFPIA (2022). The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines. Available here.
[41] Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Available here.

Distinct from those general assumptions, the logic underlying the Commission's proposal fails to account for dynamics specific to rare diseases:

- One is the use of OME as an incentive to encourage broader and swifter launch and effective negotiation at Member State level. The appropriateness of this is subject to question, as OME is intended as a regulatory incentive to encourage development in areas acknowledged to be especially challenging, and is not designed as a mechanism to drive launch decisions.
- Further, there is a lack of nuance with the Commission's proposal to account for the specificities of rare diseases. It is estimated that most rare diseases (~85%) have a point prevalence of fewer than one in one million individuals.[42] Hence, it is fair to assume that some diseases with approved products are so rare that there may not be identified patients in every Member State in the EU, in which case launching would not make sense.

As a result of the above, it is unlikely that the Commission's proposal will drive broader access to OMPs in the short term. That the Parliament proposes to remove the launch conditionality altogether may suggest a possible recognition of the lack of feasibility and/or overall appropriateness of this incentive. Further, the Parliament propose to require that Member States actively request the product, which serves as a more accurate reflection of their role as a key actor in the process of securing timely reimbursement and access. By taking a more holistic approach, the Parliament's draft proposal represents a step in the right direction towards addressing this challenge.

Impact area 2. Impact on future availability of innovative OMPs in Europe:

It is unclear if full EU market launch within 2 years is feasible in practice, particularly for rare diseases owing to the scarcity of patients and high-cost drugs which may not be a priority for some Member States. The resulting uncertainty around the eligibility of the incentive is therefore unlikely to materially change the attractiveness of investing in development and launch of OMPs in Europe. In practice, the proposal will add further to the regulatory burden for market authorisation holders, which may drive investment away from Europe and therefore hamper future availability of new OMPs.

Impact area 3. Implementation considerations for Member States:

Following from the sections above, it is unlikely that Member States will see a significant change in the breadth and speed of launch of OMPs because of the Commission's proposal.

In terms of operations, both the Commission's proposal and Parliament's draft proposal would likely involve procedural changes to either waive or request dossier submission within the allotted timeframe, which would consume time and capacity of Member State authorities. Also, in the event of a large increase in the number of P&R applications, this might stretch existing resources, especially for smaller Member States with limited HTA capabilities and/or resourcing.

[42] Wakap et al. (2019). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Available here.

Proposal on transparency of public contributions to R&D financing

(i) Context and problem

At present, there is no requirement at the regulatory level for market authorisation holders to divulge their R&D costs or public contributions to these costs.

In their impact assessment of the GPL, the Commission refers to research costs incurred as one of many factors which influence the price of medicines. It is recognised that, while R&D costs are not relevant to the risk-benefit assessment of the medicine, information on such costs are of interest to downstream actors (not least those involved in pricing negotiations) and may aid in their decision-making.[43]

On that basis, greater transparency on R&D costs and/or public contributions to these costs is included among the policy options to improve the affordability of medicines. The logic presented by the Commission is that increased transparency around public support for medicine development may strengthen payers' bargaining position, and ultimately help improve access to affordable medicines by placing downward pressure on prices.[44]

(ii) Commission proposals

The Commission proposes that marketing authorisation holders are required to publish all direct financial support received from any public authority or publicly funded body for all R&D activities for the product, whether successful or unsuccessful.[45] (Note the draft proposal by the Parliament amends this so it would only apply to public funding received from EU sources).[46]

(iii) Impact assessment and discussion

Impact area 1. Capacity to improve OMP access and affordability in the short term:

A primary assumption underpinning this proposal is that public financing makes up a non-trivial proportion of R&D spending for a specific product. However, owing to the enormity of private investment involved in developing and bringing a drug to market, this is unlikely to be the case. A recent US-based study comparing National Institute for Health (NIH) funding to private investment in the development of 18 FDA-approved medicines finds that public funding accounted for only ~1% of investment overall.[47] Assuming circumstances are similar in Europe, it is unlikely that highlighting this investment will significantly improve payers' position in negotiations with marketing authorisation holders.

A second key assumption is that developers can readily determine the amount of public investment in R&D attributable to a single product, but there are numerous practical challenges to arriving at this number:

- There is a lack of generally accepted methodology for apportioning investment to specific products, which are often developed over many years or decades via a large number pre-clinical and clinical studies, many of which fail. The Commission's proposal includes 'cost of failures', but there is little clarity on how this should be captured, hence risking that investment in medicines that never get approved is not accounted for.

[43] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 1/2). Available here.
[45] European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 1/2). Available here.
[45] European Commission (2023). Proposal for the Pharmaceutical Directive. Available here.
[46] European Parliament (2023). Draft Report (2023/0131(COD)). Available here.
[47] Vital Transformation (2021). Who Develops Medicines?: An Analysis of NIH Grants. Available here.

- R&D is generally global in nature, particularly in rare diseases where patients are scarce and geographically distributed. This means that mapping the interaction between investments and R&D activities across regions poses additional challenges in practice.

In the absence of a clear methodology, it is unlikely that developers can reliably fulfil the proposed requirement, nor that the results are easily interpreted by Member States for the purpose of informing decisions. Combined with the fact that the number may not be very impactful, there is even less chance that increased transparency will yield the affordability benefit assumed.

Impact area 2. Impact on future availability of innovative OMPs in Europe:

The impact of this proposal on the innovation environment in Europe depends on its application. For instance, if used to support cost-plus pricing within country-level P&R, this would fail to capture the full value of OMPs and, over time, reduce the economic viability developing and launching new products in Europe. To the extent that proposals discourage industry investment in this, Member States will be impacted in the form of patients having fewer options and potentially worse outcomes relative to patients in other regions.

While only a small proportion of clinical stage development is funded by public actors, pre-clinical discovery largely relies on academic centres and/or public-private partnerships. Depending on the reach of this proposal, it may discourage such partnerships that are often the outset of potential new treatments.

Impact area 3. Implementation considerations for Member States:

If Member States wish to utilise R&D transparency to inform P&R decisions, competent authorities would need to define how to integrate this into existing frameworks. Further, a process would be needed across Member States to define appropriate methodology and verification mechanisms for R&D tracking, which promises to be difficult.

Conclusion

Upwards of 36 million people in Europe are living with a rare disease.[48] The GPL revision is a once in a generation opportunity to calibrate the European regulatory system to advance timely access to innovative OMPs while securing their future availability by fostering an attractive, dynamic environment for industry to develop and launch these medicines.

Member States have a strong interest in the outcomes of the revision and its implementation where national systems, processes and requirements are impacted. This paper has sought to highlight potential areas of impact of three key proposals by the Commission aimed at improving OMP access and affordability.

Key findings in terms of Member State-level consequences include:

- Proposed reductions to OME duration and eligibility may yield cost-savings in certain cases over the short term, but likely at the expense of undermining key incentives for OMP development and launch in Europe.
- Proposed conditional OME supplements may not be sufficiently calibrated or predictable to encourage

[48] European Commission (n.d.) Rare diseases. Accessed 19 April 2024 from here.

industry to take on the considerable cost and risk of developing and launching in a HUMN area and/or pursue EU market launch within two years.

- Any changes impacting evidence availability – whether it be more (e.g. clarity on public R&D financing) or less (e.g. accelerated regulatory approval pathways, meaning lower quality evidence at launch) is likely to impact national P&R processes and carries risk of misalignment with country needs and priorities.

The potential effects of these proposals should be considered within the broader European policy context, including Member States, which together set out EU's attractiveness and competitiveness. The GPL proposals will act alongside the forthcoming EU Joint Clinical Assessment process and existing national pricing and reimbursement pathways. In the former, uncertainty exists around its implementation and whether approaches will be fit for purpose for OMPs. While in the latter, there is an observed increase in use of cost-containment policies, which are targeting mainly high-cost products including OMPs.

Ensuring the right policy environment is in place is a challenge but is critical to ensure timely and sustainable access to orphan innovation. Simple, predictable, and effective regulatory incentives frameworks are needed to encourage the development of innovative drugs in high areas of unmet need. These need to be sufficient to appropriately reward the value and risk of developing OMPs, while also being compatible with long-term sustainability for health systems. In view of the transformative therapeutic breakthroughs coming to market, Europe cannot afford to fall out of step in the development, regulation, and provision of rare disease medicines.

References

Blaney and Dirkzwager (2023). EU Pharma Legislation Review Series: Bolar Exemption under Patent Rights. Available: https://www.insideeulifesciences.com/2023/05/02/eu-pharma-legislation-review-series-bolar-exemption-under-patent-rights/

Dolon (2023). Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available: https://efpia.eu/media/cm2jbsjx/revision-of-the-general-pharmaceutical-legislation-impact-assessment-of-european-commission-and-efpia-proposals.pdf

Dowlat (2016). The opportunities and challenges of biosimilar orphans. Expert Opinion on Orphan Drugs, 4(6):563-566. Available: https://www.tandfonline.com/doi/full/10.1517/21678707.2016.1171142

EFPIA (2024). Imagining a future where rare diseases patients have a better chance at a healthy life. Available: https://www.efpia.eu/news-events/the-efpia-view/blog-articles/imagining-a-future-where-rare-diseases-patients-have-a-better-chance-at-a-healthy-life/#:~:text=In%20partnership%20with%20seven%20stakeholders,via%20the%20Rare%20Disease%20Moonshot

EFPIA (2022). The root cause of unavailability and delay to innovative medicines. Available: https://www.efpia.eu/media/636822/root-cause-unavailability-delays-cra-report-april-2022-final.pdf

EFPIA (2022). The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines. Available: https://www.efpia.eu/media/636822/root-cause-unavailability-delays-cra-report-april-2022-final.pdf

EFPIA (n.d.). Revision of the General Pharmaceutical Legislation: Impact Assessment of European Commission and EFPIA proposals. Available: https://www.efpia.eu/media/zcwist01/revision-of-the-general-pharmaceutical-legislation-impact-assessment-of-european-commission-and-efpia-proposals.pdf

EUCOPE (2022). EUCOPE letter on the revision of the general pharmaceutical and OMP legislation. Available: https://www.eucope.org/wp-content/uploads/2022/10/eucope-letter-on-the-revision-of-the-general-pharmaceutical-and-omp-legislation-2022-09-14.pdf

European Commission (2023). Proposal for the Pharmaceutical Regulation. Available: https://eur-lex.europa.eu/resource.html?uri=cellar:e3f40e76-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF

European Commission (2023). Proposal for the Pharmaceutical Directive. Available: https://eur-lex.europa.eu/resource.html?uri=cellar:bfcb9e00-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF

European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 1/2). Available: https://health.ec.europa.eu/document/download/027a1084-0540-4bb6-b669-aa6cf3887684_en?filename=swd_2023_192_1_ia_en.pdf

European Commission (2023). Commission Staff Working Document – Impact Assessment Report (Part 2/2). Available: https://eur-lex.europa.eu/resource.html?uri=cellar:d75b91b3-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_2&format=PDF

European Commission (2020). Commission Staff Working Document – Evaluation of the Regulation No 469/2009. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020SC0292

European Commission (2020). Commission Staff Working Document – Joint evaluation of Regulations No 1901/2006 and 141/2000. Available: https://health.ec.europa.eu/document/download/386fb8fa-7633-482b-bd1b-5d2a492c9be7_en?filename=orphan-regulation_eval_swd_2020-163_part-1.pdf

European Commission (2014). Implementation report on the Commission Communication on Rare Diseases: Europe's Challenges. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:52014DC0548

European Commission (n.d.). Orphan medicinal products. Available: https://health.ec.europa.eu/medicinal-products/orphan-medicinal-products_en

European Commission (n.d.) Rare diseases. Available: https://health.ec.europa.eu/european-reference-networks/rare-diseases_en

European Medicines Agency (n.d.). Legal framework: orphan designation. Available: https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview/legal-framework-orphan-designation

European Medicines Agency (n.d.). Orphan incentive. Available: https://www.ema.europa.eu/en/human-regulatory-overview/research-development/orphan-designation-research-development/orphan-incentives#:~:text=Authorised%20orphan%20medicines%20benefit%20from,indications%20once%20they%20are%20approved

European Parliament (2023). Draft Report (2023/0131(COD)). Available: https://www.europarl.europa.eu/doceo/document/ENVI-PR-753550_EN.pdf

EURORDIS (2023). Revisions for the better: How Europe should boost the development of rare disease medicines. Available: https://www.eurordis.org/revisions-for-the-better/

Heads of HTA Agencies Group (2024). Joint position statement on the Commission's proposal. Available: https://htahag.eu/wp-content/uploads/2024/02/HAG-short-position-on-EU-Pharma-reform_FINAL.pdf

Neez and Hutchings (2023). Revision of the Orphan Regulation: Estimated impact on incentives for innovation of changes proposed by the European Commission. Available: https://dolon.com/wp-content/uploads/2023/09/Impact-of-changes-to-Orphan-Regulation-Dolon-Report.pdf?x58108

Neez et al. (2021). Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions. Available: https://dolon.com/dolon/wp-content/uploads/2021/07/Addressing-unmet-needs-in-extremely-rare-and-paediatric-onset-diseases.pdf

Lancet (2019). Spotlight on rare diseases. Available: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(19)30006-3/fulltext#:~:text=As%20there%20is%20no%20approved,on%20patients%20and%20their%20caregivers

Pakter, P. (2024). Rare disease care in Europe – Gaping unmet needs. Rare, 2:100018. Available: https://doi.org/10.1016/j.rare.2024.100018

Rare2030 (2021). Recommendations from the Rare 2030 Foresight Study: The Future of Rare Diseases Starts Today. Available: https://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN

Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Available: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R2282

Vital Transformation (2021). Who Develops Medicines?: An Analysis of NIH Grants. Available: https://vitaltransformation.com/wp-content/uploads/2021/05/V.T.-NIH-Grants-Analysis-5-10-2021_FINAL_v4.pdf

Wakap et al. (2019). Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics 28:165–173. Available: https://www.nature.com/articles/s41431-019-0508-0

Wouters et al. (2017). Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending. The Milbank Quarterly, 95(3):554-601. Available: https://onlinelibrary.wiley.com/doi/10.1111/1468-0009.12279